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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,267	11/22/2005	Kevin J. Tracey	3268.1003-004	6690

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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06/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,267	TRACEY, KEVIN J.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-9 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 6 and 10-45 are cancelled.

   Claim 1 has been amended.

   Claim 46 has been added.

2. Claims 1-5, 7-9 and 46 are pending and under consideration.

3. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

4. The objection to the title of the invention as clearly indicative of the invention to which the claims are directed is withdrawn in view of the newly submitted title filed 3/6/09.

5. The rejection of claim 6 under 35 U.S.C. 112, first paragraph, while being enabling for a composition comprising a polypeptide comprising an HMGB B box comprising the amino acid sequence of SEQ ID Nos:5, 20 or 45 and does not comprise an HMGB A box, wherein the HMGB B box is mammalian, human or is a HMGB1 B box and further comprising an adjuvant, does not reasonably provide enablement for a pharmaceutical composition comprising a therapeutically effective amount of a polypeptide comprising an HMGB B box or a functional variant thereof and does not comprise an HMGB A box, wherein said polypeptide increases an immune response in an individual administered said pharmaceutical composition and wherein the HMGB B box is mammalian, human or is a HMGB1 B box and the pharmaceutical composition further comprises a vaccine, or an adjuvant selected from one or more immunostimulatory oligonucleotides comprising unmethylated CpG sequences, an imidazoquinoline, monophosphoryyl lipid A and detoxified lipopolysaccharide as broadly encompassed by the claims is withdrawn in view of the cancellation of the claim.

6. The rejection of claims 1-2 and 4-5 under 35 U.S.C. 102(a) as being anticipated by Taudte et al (Protein Engineering, 14(2):1015-1023, December 2001, IDS reference C69 filed 6/5/06) is withdrawn in view of the amendments to the claims.

7 The rejection of claims 1-2 and 4-5 under 35 U.S.C. 102(b) as being anticipated by Bianchi et al (The EMBO Journal, 11(3):1058-1063, 1992, IDS reference C11 filed 6/5/06) is withdrawn in view of the amendments to the claims.

8. The rejection of claims 1-5 and 7 under 35 U.S.C. 102(e) as being anticipated by Tracey et al (US 2003/0144201 A1, priority to 5/15/2001, IDS reference A6 filed 6/5/06) is withdrawn in view of the amendments to the claims.

Rejections Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The rejection of claims 1-5, 7-9 and now applied to newly added claim 46 under 35 U.S.C. 112, first paragraph, while being enabling for a composition comprising a polypeptide comprising an HMGB B box comprising the amino acid sequence of SEQ ID Nos:5, 20 or 45 and does not comprise an HMGB A box, wherein the HMGB B box is mammalian, human or is a HMGB1 B box and further comprising an adjuvant, does not reasonably provide enablement for a pharmaceutical composition comprising a therapeutically effective amount of a polypeptide comprising an HMGB B box or a functional variant thereof and does not comprise an HMGB A box, wherein said polypeptide increases an immune response in an individual administered said pharmaceutical composition and wherein the HMGB B box is mammalian, human or is a HMGB1 B box and the pharmaceutical composition further comprises a vaccine, or an adjuvant selected from one or more immunostimulatory oligonucleotides comprising unmethylated CpG sequences, an imidazoquinoline, monophosphoryyl lipid A and detoxified lipopolysaccharide as broadly encompassed by the claims is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The response filed 3/6/09 states that the claims are directed to compositions and not methods of treatment, such as treating cancer or viral infections and thus, whether or not applicants' claimed compositions are enabled in a method for treating patients with cancer, viral

infections, or other diseases, should not be at issue in the pending application. This has been fully considered but is not found persuasive. Compliance with the enablement requirement of the first paragraph of 35 USC 112, requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The statute makes clear that:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Thus, applicants' argument suggesting that the specification need not teach how to make and use the claimed compositions is not found persuasive. The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'. " *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Applicant argues that whether a "therapeutic will be safe and tolerable for anyone susceptible to the disease" (pg. 7 of the previous Office Action) is more properly regulated by the FDA, citing MPEP 2107 for support. The examiner agrees that FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed.Cir. 1994). Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. The proper context of the line from the previous Office Action quoted by Applicant was to show that applicant has not provided sufficient guidance or direction to assist those skilled in the art in making and using a vaccine of the claimed composition for preventing and curing cancer and viral infections consistent with the disclosed utilities, i.e., how to use the claimed compositions.

With respect to the genus of polypeptides comprising an HMGB B box or a functional variant thereof, Applicant argues that only routine experimentation would be required to practice the claimed invention when guided by applicants' specification and what was known at the time of filing. Applicant refers to Example 2 of the specification as disclosing guidance for identifying B box domain in an HMGB polypeptide and disclosed several examples of specific amino acid sequences for HMGB B boxes (pp. 11-12). Applicant also notes that the specification also describes HMGB B box fragments that do not have functional activity (pg. 32 and Fig 3). Applicants' arguments have been fully considered but are not found persuasive. The specification discloses that HMGB B box polypeptides of the invention also encompass sequence variants and functional variants, including allelic variants and variants having at least 60% sequence identity to the disclosed HMGB B box (e.g., at least 60% sequence identity to SEQ ID Nos:5, 20 and 45) (e.g., see pp. 12-13). Thus, the scope of the claims embraces polypeptides comprising an HMGB B box and a "functional variant thereof" encompassing sequence variants and functional variants, including allelic variants and variants having at least 60% sequence identity to the disclosed HMGB B box. The teachings and exemplary guidance referred to by applicant does not provide any guidance or direction to assist the skilled artisan in using a pharmaceutical composition comprising a vaccine and just any HMGB B box polypeptide, including HMGB B box polypeptide variants and functional variants, including allelic variants and variants having at least 60% sequence identity to the disclosed HMGB B box (e.g., at least 60% sequence identity to SEQ ID Nos:5, 20 and 45) for the treatment or prevention of cancer or a viral infection.

"[T]o be enabling, the specification.., must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright,* 999 F.2d at 1561, 27 USPQ2d at 1513 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck,* 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138 (Fed. Cir. 1999).

"Patent protection is granted in return for an enabling disclosure..., not for vague intimations of general ideas that may or may not be workable." *Genentech,* 108 F.3d at 1365, 42 USPQ2d at 1005. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." Id. at 1366, 42 USPQ2d at 1005 (emphasis added).

Applicants provide little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the disclosed HMGB B box polypeptides of SEQ ID Nos:5, 20 and 45 that are tolerant to change and the nature and extent of changes that can be made in these positions. Further, the state of the prior art also recognizes that the administration of an HMGB1 polypeptide triggers an inflammatory cascade, which activates inflammatory responses that can cause tissue damage and even death. See Fig. 4 of Yang et al (Journal of Leukocyte Biology, 78:1-8, July 2005, cited on PTO-892 mailed 9/3/08). Yang et al also teach that administration of HMGB1 into mice joints induces arthritis changes and stimulated the synovial macrophages to release proinflammatory cytokines including TNF, IL-1β and IL-6, indicating that HMGB1 plays a pathogenic role in arthritis (pg. 5). Andersson et al (Journal of Leukocyte Biology, 72:1084-1091, December 2002, cited on PTO-892 mailed 9/3/08) teaches that HMGB1 is a mediator of acute inflammatory lung injury and to elucidate the importance of extracellularly released HMGB1 in the pathogenesis of human diseases and to plan for future therapeutic intervention, there are a number of basic questions to resolve (see pg. 1089, "Lung Inflammation" and "Future Perspectives"). Andersson et al also poses the question, will HMGB1 be validated as a clinical target, like TNF or IL-1, to modulate acute or chronic inflammation, or will it be too dangerous to interfere with a molecule that is so central for the interplay between necrotic cell death with subsequent inflammation and repair response? (see pg. 1090).

One of ordinary skill in the art could not predictably extrapolate the teachings, guidance and exemplification in the specification limited to HMGB B box polypeptides comprising a human HMGB1 B box comprising SEQ ID NO:5, 20 or 45 (which are three different lengths of

the human HMGB1 B box) and which potently induce TNF production to the full scope of the claims encompassing pharmaceutical compositions comprising a large genus of HMGB B box polypeptides and functional variants thereof (i.e., at least 60% identity) that induce an immune response and are useful for the treatment and/or prevention of cancer or a viral infection (e.g., HIV/AIDS), particularly in view that HMGB1 triggers an inflammatory cascade, which activates inflammatory responses that can cause tissue damage and even death, and HMGB1 plays a pathogenic role in arthritis and is implicated in acute inflammatory lung injury and in view of the uncertainty in the art (e.g., Andersson et al, supra) whether it will be too dangerous to interfere with HMGB1, which is so central for the interplay between necrotic cell death with subsequent inflammation and repair response.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Skolnick et al, Metzler et al, Mikayama et al, Burgess et al, Yang et al, Andersson et al, Ezzell et al, Forni et al, Donnelly J. and DeGruijl et al (all of record), the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed HMGB B box pharmaceutical compositions and vaccines with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed HMGB B box pharmaceutical compositions and vaccines and absent working examples providing evidence which is reasonably predictive that the claimed HMGB B box pharmaceutical compositions and vaccines are therapeutically effective, commensurate in scope with the claimed invention.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643